BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03885.x

Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women

Matt S. Anderson,[1] William D. Hanley,[1] Allison R. Moreau,[1] Bo Jin,[1] Frederick A. Bieberdorf,[2]* James T. Kost,[1] Larissa A. Wenning,[1] Julie A. Stone,[1] John A. Wagner[1] & Marian Iwamoto[1]

[1]Merck Research Labs, Merck & Co., Inc., Whitehouse Station, NJ, USA and [2]Principal investigator, CEDRA Clinical Research, Austin, TX, USA

Correspondence
Dr Matt S. Anderson, Merck Research Laboratories, RY34-A500, 126 E. Lincoln Avenue, Rahway, NJ 07065-0900, USA.
Tel.: +1 732 593 3801
Fax: +1 732 594 5405
E-mail: matt_anderson@merck.com

*Dr F. A. Bieberdorf died 19 April 2009.

Keywords
drug–drug interaction, ethinyl estradiol, HIV-1, oral contraceptive, raltegravir

Received
27 April 2010

Accepted
23 October 2010

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Oral contraceptives are a widely prescribed means of birth control that requires the maintenance of adequate pharmacokinetics of the active components to maintain efficacy.
- Oral contraceptive use in HIV-infected women is widespread and may often occur in women receiving raltegravir as part of their antiretroviral therapy.
- Given the prevalence of oral contraceptive use and likely need for co-administration with raltegravir, combination administration should be studied to assess the safety and the pharmacokinetics of the oral contraceptive components.

WHAT THIS STUDY ADDS

- This study is the first to provide the practitioner with a detailed description of the influence of raltegravir on the pharmacokinetics of a triphasic oral contraceptive.
- This study demonstrates that raltegravir does not meaningfully alter the pharmacokinetics of the estrogen or progestin components of such oral contraceptives.
- This paper provides confidence to the practitioner that there will be no clinically meaningful interaction that would preclude the concurrent use of raltegravir and such oral contraceptives in combination.

AIMS

Oral contraceptives such as norgestimate–ethinyl estradiol (Ortho Tri-Cyclen®) are commonly prescribed in the HIV-infected patient population. A placebo-controlled, randomized, two-period crossover study in healthy HIV-seronegative subjects was conducted to assess the effect of raltegravir on the pharmacokinetics of the estrogen and progestin components of norgestimate–ethinyl estradiol [ethinyl estradiol (EE) and norelgestromin (NGMN), an active metabolite of norgestimate (NGT)].

METHODS

In each of two periods, nineteen healthy women established on norgestimate–ethinyl estradiol contraception (21 days of active contraception; 7 days of placebo) received either 400 mg raltegravir or matching placebo twice daily on days 1–21. Pharmacokinetics were analysed on day 21 of each period.

RESULTS

The geometric mean ratio (GMR) and 90% confidence interval (CI) for the EE component of norgestimate–ethinyl estradiol when co-administrated with raltegravir relative to EE alone was 0.98 (0.93–1.04) for the area under the concentration–time curve from 0 to 24 h ($AUC_{0-24\,h}$) and 1.06 (0.98–1.14) for the maximum concentration of drug in the plasma (C_{max}); the GMR (90% CI) for the NGMN component of norgestimate–ethinyl estradiol when co-administered with raltegravir relative to NGMN alone was 1.14 (1.08–1.21) for $AUC_{0-24\,h}$ and 1.29 (1.23–1.37) for C_{max}. There were no discontinuations due to a study drug-related adverse experience, nor any serious clinical or laboratory adverse experience.

CONCLUSIONS

Raltegravir has no clinically important effect on EE or NGMN pharmacokinetics. Co-administration of raltegravir and an oral contraceptive containing EE and NGT was generally well tolerated; no dose adjustment is required for oral contraceptives containing EE and NGT when co-administered with raltegravir.

Introduction

Raltegravir (ISENTRESS®, Merck & Co., Inc., Whitehouse Station, NJ, USA) is an HIV-1 integrase strand transfer inhibitor for use in treatment-experienced and treatment-naïve HIV-1-infected individuals, including women of child-bearing potential [1]. Oral contraceptive (OC) use in HIV-infected women is widespread [2]. Given the likelihood of co-administration, a clinical drug interaction study of raltegravir and a triphasic OC was conducted in healthy women.

As a widely prescribed combination OC, norgestimate–ethinyl estradiol (NGT/EE; Ortho Tri-Cyclen®, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, USA) was selected for investigation. EE undergoes extensive first-pass metabolism through sulfation and to a lesser extent by oxidation and glucuronidation [3]. In the systemic circulation, EE is largely metabolized through oxidative metabolism catalysed by cytochrome P450 (CYP) 3A [4]. NGT is rapidly metabolized to several metabolites, including norelgestromin (NGMN), the main contributor to progestin activity [5].

Raltegravir is not a known inducer or inhibitor of major CYP isoforms and other drug-metabolizing enzymes and is not metabolized through CYP-mediated oxidation [1]. Thus, raltegravir was not expected to influence the pharmacokinetics of either EE or NGMN. This study evaluated the safety and tolerability of co-administered raltegravir and NGT/EE, and the effect of raltegravir on the pharmacokinetics of EE and NGMN.

Methods

Healthy nonpregnant, non-obese, female subjects (18–45 years old) who were receiving either Ortho Tri-Cyclen® or the generic equivalent were eligible. Subjects were required to use barrier contraceptive methods during the study. All subjects provided written informed consent to participate in the study. The protocol was approved by the institutional review board of the study centre (IntegReview Ethical Review Board). The protocol was conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki.

In a randomized crossover fashion in two 28 day treatment periods, subjects received NGT/EE daily with 400 mg raltegravir or matching placebo tablet every 12 h on days 1–21 as follows: phase I (days 1–7), EE 0.035 mg, NGT 0.180 mg; phase II (days 8–14), EE 0.035 mg, NGT 0.215 mg; and phase III (days 15–21), EE 0.035 mg, NGT 0.25 mg. The placebo component of NGT/EE was administered on days 22–28. Day 21 treatment was administered in the fasted state. Due to an error, no evening raltegravir dose was given on day 21 of period 1 or 2. The implications of this omission are discussed below. Raltegravir or matching placebo was administered in a blinded manner.

Analytical and pharmacokinetic measurements

Both EE and NGMN were assessed predose and on day 21 predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h postdose. Samples were analysed by Pharmaceutical Product Development, Inc. (Richmond, VA, USA) as previously reported [6].

The area under the concentration–time curve from 0 to 24 h ($AUC_{0-24\,h}$) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. Values for the maximum concentration of drug in the plasma (C_{max}) and time to reach C_{max} (T_{max}) were obtained by inspection.

Statistical methods

The AUC and C_{max} values were natural-log-transformed before analysis. Exponentiation was performed on the means (mean differences) and lower and upper limits of these confidence intervals prior to reporting. Statistical analyses were conducted using SAS version 8 (SAS Institute Inc., Cary, NC, USA). With the exception of T_{max}, all confidence intervals were based on the least-squares means and variance components arising from a linear mixed-effect model appropriate for a two-period crossover design, with fixed effect terms for sequence, period and treatment and a random effect term for subject-within-sequence.

As appropriate, 90% confidence interval was constructed for geometric mean ratios (GMR; with raltegravir/without raltegravir). For T_{max}, the Hodges–Lehman estimate of the median difference (with raltegravir minus without raltegravir) was computed, as were the corresponding 90% confidence intervals.

Results

Twenty female subjects were enrolled with a mean weight of 66.9 kg (range, 51.2–89.2 kg) and a mean age of 27.3 years (range, 18–38 years). Eighteen of the 20 enrolled subjects were Caucasian and two were Hispanic.

Nineteen subjects completed the study per protocol. One subject withdrew consent following a clinical adverse experience of otitis media, considered not related to either study drug, and withdrew from the study. The pharmacokinetic data for this subject were incomplete and were not included in the final pharmacokinetic analysis. Safety data up to discontinuation were recorded in the final safety analysis.

The EE and NGMN plasma concentration–time profiles are shown in Figure 1A,B, respectively. The model-based geometric means of EE and NGMN are provided in Table 1.

The evening dose of raltegravir on day 21 of both periods was erroneously omitted. To evaluate the full effect

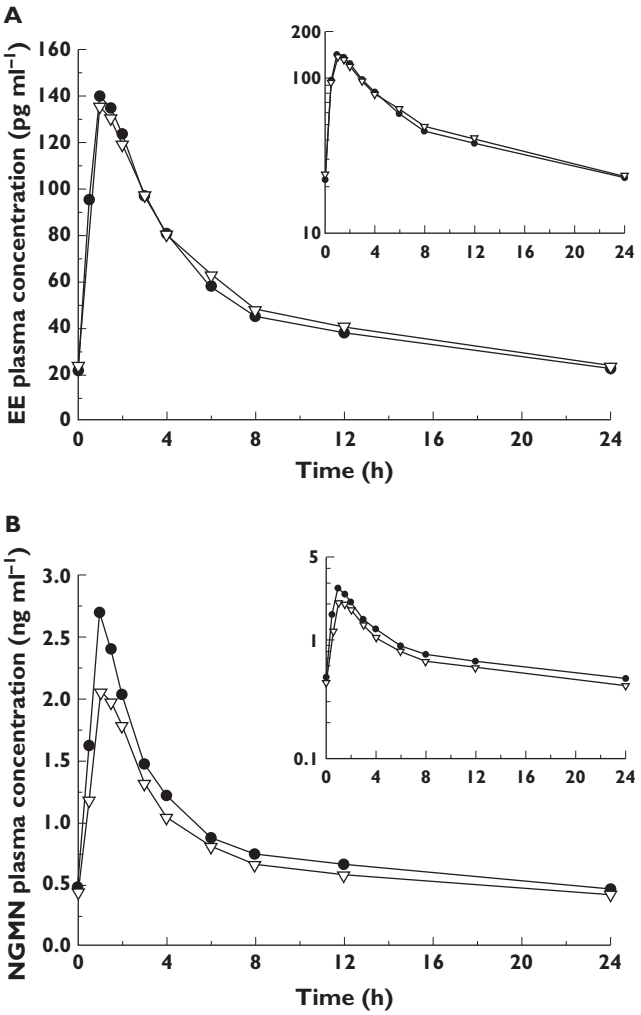

Figure 1

Arithmetic mean plasma ethinyl estradiol (A) and norelgestromin concentration profiles (B) on day 21 following multiple doses of norgestimate/ethinyl estradiol once daily with or without 400 mg of raltegravir every 12 h to healthy women ($n = 19$). Insets show the data plotted on a semilogarithmic scale. Ortho Tri-Cyclen® + Raltegravir (—●—); Ortho Tri-Cyclen® + PBO (—▽—)

of raltegravir on EE and NGMN pharmacokinetics over the 24 h dosing interval, both morning and evening doses on day 21 would have to have been administered. However, this error was not considered to have a major impact on the results; for the oral contraceptive components examined, the majority of the AUC (approximately 70%) was observed during the first 12 h postdose. In order to further address the potential implications of this dosing error, we also examined the effect of raltegravir on the $AUC_{0-12\,h}$ for EE and NGMN. The geometric means, geometric mean ratios and corresponding confidence intervals for $AUC_{0-12\,h}$ for EE and NGMN administered with placebo and in combination with raltegravir were compared and revealed no meaningful differences in the AUC of either EE or NGMN as

Table 1

Comparison of ethinyl estradiol and norelgestromin plasma pharmacokinetics following administration of multiple doses of Ortho Tri-Cyclen® with or without multiple doses of 400 mg raltegravir twice daily to healthy women

Pharmacokinetic parameter	*n*	Ortho Tri-Cyclen® + raltegravir Geometric mean*	95% Confidence interval for geometric mean	Ortho Tri-Cyclen® + placebo Geometric mean*	95% Confidence interval for geometric mean	Ortho Tri-Cyclen® + raltegravir /Ortho Tri-Cyclen® + placebo Geometric mean ratio	90% Confidence interval for geometric mean	*P*-value†
Ethinyl estradiol (EE)								
$AUC_{0-24\,h}$ (pg h ml^{-1})	19	1139.10	(1088.2–1192.3)	1158.71	(1107.0–1212.9)	0.98	(0.93–1.04)	0.5843
$AUC_{0-12\,h}$ (pg h ml^{-1})	19	800.47	(767.4–835.0)	811.55	(778.0–846.5)	0.99	(0.94–1.04)	0.6334
C_{max} (pg ml^{-1})	19	143.63	(134.6–153.3)	136.13	(127.6–145.3)	1.06	(0.98–1.14)	0.2351
T_{max} (h)‡§	19	1.00	(1.00–2.00)	1.00	(1.00–1.50)	0.00	(–0.50 to 1.00)	–
Norelgestromin (NGMN)								
$AUC_{0-24\,h}$ (ng h ml^{-1})	19	19.51	(18.5–20.5)	17.05	(16.2–17.9)	1.14	(1.08–1.21)	0.0011
$AUC_{0-12\,h}$ (ng h ml^{-1})	19	13.14	(12.5–13.8)	11.36	(10.8–11.9)	1.16	(1.09–1.22)	0.0003
C_{max} (ng ml^{-1})	19	2.72	(2.6–2.8)	2.10	(2.0–2.2)	1.29	(1.23–1.37)	<0.0001
T_{max} (h)‡§	19	1.00	(0.50–2.00)	1.00	(1.00–6.00)	–0.25	(–1.00 to 0.00)	–

*Geometric mean computed from least-squares estimate from the mixed model performed on the natural-log-transformed values. †*P*-value for the hypothesis that the true GMR is equal to one. ‡Median (minimum, maximum) provided for T_{max}. §Median difference and confidence interval from Hodges–Lehmann estimation reported for T_{max}. CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio.

shown in Table 1. As T_{max} for EE and NGMN occurred prior to 12 h postdose, the analysis for C_{max} was unaffected by the interval used.

Raltegravir dosed in combination with NGT/EE was generally well tolerated. No serious clinical or serious laboratory adverse experiences were reported. One subject withdrew consent due to a clinical adverse experience judged as unrelated to the study drug. Six of the 20 subjects enrolled reported eight nonserious clinical adverse experiences, one of which (nausea) was determined by the investigator as possibly drug related. All clinical adverse experiences reported were generally transient and rated as mild or moderate in intensity. No laboratory adverse experiences were reported.

Discussion

These data indicate that multiple dose administration of raltegravir has no clinically meaningful effect on the pharmacokinetics of either the estrogen or the progestin components of Ortho Tri-Cyclen®. The parameters for EE ($AUC_{0-24\,h}$ and C_{max}) were essentially unchanged, while the $AUC_{0-24\,h}$ of NGMN was increased only marginally (14%). The NGMN C_{max} increased by 29%. Given these minimal changes under an OC regimen bearing 0.035 mg EE, users of low-dose estrogenic monophasic OCs containing 0.015–0.020 mg of estrogen should likewise be unaffected.

The biological basis for the modest difference in C_{max} is currently unknown, but could potentially stem from a difference in the rate of absorption of the precursor, NGT, or from a small difference in the metabolic conversion of NGT to NGMN. A recent study to examine the frequency of reported symptoms by oral contraceptive pill composition among French women revealed that with the exception of a lower frequency of back pain during menstrual periods, of the several EE plus progestin regimens available, there was no difference in reported symptoms according to the sequence of administration (monophasic, biphasic or triphasic) [7]. Likewise, there were very few differences in reported symptoms by women using the same estrogen dosage with different types of progestin components in third-generation OC pills [7]. This implies that a range of progestin pharmacokinetic profiles over a contraceptive cycle results in virtually no change in safety profiles. Additionally, pharmacokinetic studies were conducted for NGMN administered transdermally across varying anatomical sites [8]. Exposure and C_{max} variations were seen with an increase of up to approximately 30% relative to the control site. This variation was not deemed clinically relevant, with the basis of clinical relevance defined by a target steady-state concentration reference range. Thus, it is likely that the approximately 30% elevation in NGMN C_{max} is of minor relevance with regard to safety and efficacy margins for NGMN and contributes an insignificant change to NGMN exposures overall as evidenced by the lack of a clinically meaningful change in the associated pharmacokinetic parameter, AUC.

The results of this study indicate that it is highly unlikely that co-administration of NGT/EE with raltegravir will alter the effectiveness of NGT/EE as a contraceptive. Additionally, the combination of raltegravir with EE and NGMN has a favourable safety profile. Thus, the combined safety and pharmacokinetic data support the co-administration of raltegravir with triphasic oral contraceptives without dose adjustment.

Competing Interests

MA, WD, AM, BJ, JK, LW, JS, JW and MI are employees of Merck & Co., Inc., may own stock and/or stock options in the company. FB received grant support, consultant fees and/or lecture honoraria.

Previous presentation of information

Some of the information in this manuscript has been presented as a poster:

Anderson MS, Wenning LA, Moreau A, Kost JT, Bieberdorf FA, Stone JA, Azrolan N, Iwamoto M, Wagner JA. Effect of raltegravir (RAL) on the pharmacokinetics (PK) of oral contraceptives. *47th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Chicago, IL, 2007. Abstract no. A- 1425.

This study was funded by Merck & Co., Inc., which reviewed and provided comments on a penultimate version of this manuscript.

The authors wish to thank the study participants and study staff whose involvement made this work possible.

We also thank Jon Stek (Merck & Co., Inc.) for his assistance with editing/formatting.

REFERENCES

1 Merck and Co. I. Isentress package insert. 2008.

2 Curtis KM, Chrisman CE, Peterson HB. Contraception for women in selected circumstances. Obstet Gynecol 2002; 99: 1100–12.

3 Hirai S, Hussain A, Haddadin M, Smith RB. First-pass metabolism of ethinyl estradiol in dogs and rats. J Pharm Sci 1981; 70: 403–6.

4 Newburger J, Castracane VD, Moore PH Jr, Williams MC, Goldzieher JW. The pharmacokinetics and metabolism of ethinyl estradiol and its three sulfates in the baboon. Am J Obstet Gynecol 1983; 146: 80–7.

5 Hammond GL, Abrams LS, Creasy GW, Natarajan J, Allen JG, Siiteri PK. Serum distribution of the major metabolites of norgestimate in relation to its pharmacological properties. Contraception 2003; 67: 93–9.

6 Wong FA, Edom RW, Duda M, Tischio JP, Huang M, Juzwin S, Tegegne G. Determination of norgestimate and its metabolites in human serum using high-performance liquid chromatography with tandem mass spectrometric detection. J Chromatogr B Biomed Sci Appl 1999; 734: 247–55.

7 Moreau C, Trussell J, Gilbert F, Bajos N, Bouyer J. Oral contraceptive tolerance: does the type of pill matter? Obstet Gynecol 2007; 109: 1277–85.

8 Abrams LS, Skee DM, Natarajan J, Wong FA, Anderson GD. Pharmacokinetics of a contraceptive patch (Evra/Ortho Evra) containing norelgestromin and ethinyloestradiol at four application sites. Br J Clin Pharmacol 2002; 53: 141–6.